REMARKS

The new claims are supported at, e.g., page 7, lines 4-12 and page 11, lines 26-36.

The examiner has requested scientific evidence which supports the conclusions submitted by Prof. Sekiguchi, the main inventor of the cited Japanese applications. Applicants, however, remain of the position that the previous assertions of fact by Professor Sekiguchi in declaration format were sufficient to establish the novelty of the claims over the cited Japanese publications. Nevertheless, the accompanying additional declaration by Prof. Sekiguchi provides the requested evidence.

The latter supports the prior statements by Prof. Sekiguchi, demonstrating that the antibodies prepared in the two cited Japanese applications are not specific for an epitope in the ED-B domain of fibronectin (see page 9, lines 24-31). Details of the experiments are discussed in paragraphs 6 and 7 of the declaration. Consequently, all the prior art rejections based on these references are untenable and must be withdrawn.

The examiner has made new rejections alleging that the claims are anticipated and obvious over USP 4,894,326 (alone or in combination with other references). These rejections are based on the allegation that US '326 discloses antibodies specific for the ED-B domain of fibronectin. However, this allegation is also incorrect.

Firstly, Matsuura et al. (US '326) does not state that its antibody (FDC-6) is specific for the oncofetal ED-B domain of fibronectin. Rather, as the passages cited by the examiner show, Masuura characterizes its antibody as defining an oncofetal structure located in the fibronectin region between two sub-domains in the COOH-terminal region. This already hints that FDC-6 is not specific for the ED-B domain. Note, for example, Figure 2A of the above-identified application which shows the location of ED-B domain. It is not in the COOH terminal region.

Matsuura himself confirms the fact that his FDC-6 antibody is specific for a region of oncofetal fibronectin other than the ED-B domain. See the attached copy of Matsuura et al., J.Bio.Chem., Vol. 263, no. 7, 3314-3322, 1988. This confirms that the FDC-6 antibody defines a structure, not at the ED-B domain, but rather at "type III connecting segment (III CS)" which "is characteristic of oncofetal fibronectin." See, for example, the second sentence of the abstract.

In hopes of clarifying the situation further, applicants present the attached five page PowerPoint illustration of fibronectin structures. The first page shows the structure of normal fibronectin. As can be seen, it is devoid of the ED-B domain. As well, its III CS domain is not glycosylated. The second page demonstrates two isoforms known for oncofetal fibronectin. One is that involved in this invention where ED-B is present. The second is that involved in the work of Matsuura where ED-B is not present but the III CS domain becomes glycosylated ("g").

Slide three shows that normal fibronectin has epitopes which are present in the molecule, but because of their specific location in a conformational structure of the protein, are not accessible to antibodies specific to such epitopes. Among such antibodies are those discussed of record in this application, i.e., BC-1, CF-525 and TFN-01. However, as shown on the fourth slide, in the oncofetal fibronectin of the type where the ED-B domain is present (B^+), the structure of the protein is changed by the presence of the new domain (ED-B). As a result, epitopes previously masked become unmasked. These include the epitopes for the three mentioned antibodies, BC-1, CF-525 and TFN-01. This masking/unmasking phenomenon is what has led prior art researchers to characterize these three antibodies as being associated specifically with oncofetal fibronectin (because they do not bind to normal fibronectin), despite the fact that in reality they are specific for epitopes in normal fibronectin. They guessed that because the newly added ED-B domain was necessary for binding, these antibodies were directed to epitopes in the ED-B domain. However, it turns out that this guess was incorrect; in reality, these antibodies do not bind to the ED-B domain itself but rather to epitopes in normal fibronectin which were unmasked by the presence of ED-B. This invention was the first to provide antibodies which in fact are specific for and bind directly to the ED-B domain.

Lastly, as the fifth slide shows, the Matsuura FDC-6 antibody is specific for a fibronectin molecule which does not even contain ED-B. It binds directly to the glycosylated III CS domain of this particular type of oncofetal fibronectin. This fact is explicitly confirmed by Matsuura himself in the cited 1988 article discussed above.

As can be seen, the underpinning of all rejections, i.e., allegations that the Japanese applications and US '326 disclose antibodies specific for and directed to the ED-B domain of fibronectin, is incorrect. Thus, all prior art rejections must be withdrawn, including all rejections under 35 USC 103 since all are based on this underpinning.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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